# Non-invasive Imaging based Detection and Mapping of Brain Oxidative Stress and its Correlation with Cognative Functions

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**National Brain Research Centre**

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**Final Report**

# REPORT DOCUMENTATION PAGE

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Brain stress level measurement (non-invasively) in quantitative term is very helpful to correlate with various neuropsychological outcome. Brain protective anti-oxidant called glutathione level is affected with aging process due to increased stress. This pilot project is the first human study to measure the brain glutathione level and also perform various neuropsychological test to investigate any possible correlation between glutathione (GSH) level and neuropsychological outcome. We have found that at the age of 40 onwards, there is a depletion of brain glutathione level and these subject population (above 40Y) face more difficult to perform certain neuropsychological tests, which is easily performed by young subject (below 35Y old).

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AOARD, stress

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Non-invasive Imaging based Detection and Mapping of Brain Oxidative Stress and its Correlation with Cognitive Functions

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**Abstract:**    *Short summary of most important research results that explain why the work was done, what was accomplished, and how it pushed scientific frontiers or advanced the field. This summary will be used for archival purposes and will be added to a searchable DoD database.*

Oxidative stress is a general term used to describe the steady state level of oxidative damage in a cell, tissue, or organ, caused by the reactive oxygen species (ROS). Brain oxidative stress can have immense impact of brain health and function. Accruing evidence suggests a correlative relationship between the brain oxidative status and stress at a cellular, physiological as well as a psychological level. These stressors, in turn, have been consistently shown to impair cognitive abilities. Thus, an understanding of the link between oxidative stress and cognitive function is of immense neuroscientific importance. One of the key regulators of brain oxidative stress is the antioxidant, glutathione (GSH). GSH levels in key brain regions are an indicator of the brain oxidative status. This study aims to directly assess GSH levels in brain regions using non-invasive brain imaging, and analyze whether there exists a predictive correlation between GSH levels and cognitive performance. This pilot study provided the insight into the impact of oxidative stress on brain function, but also enable development of reliable screening tools for cognitive performance of individuals in high stress environments.

**Introduction:** *Include a summary of specific aims of the research and describe the importance and ultimate goal of the pilot study.*

Specifically, we put forth the following hypotheses:
- Brain oxidative stress levels of an individual are negatively correlated with GSH levels in the hippocampus regions.
- There is a negative correlation between brain oxidative stress and the cognitive abilities of an individual.
- GSH levels in hippocampus regions can predict cognitive function decline.

## *Objectives:*

To test the above hypotheses, we have the following research aims:
- To measure oxidative stress by quantifying the levels of the antioxidant GSH longitudinally from hippocampus, regions using multi-voxel MEGA-PRESS $^1$H MRS
- To assess the cognitive profile of the individuals through neuropsychological batteries that score their performance in various cognitive tasks.
- To determine the correlation between GSH content in the above brain regions and cognitive functions and test whether GSH levels can predict decline in cognitive functions.

**Experiment:** *Description of the experiment(s)/theory and equipment or analyses.*

In order to measure the brain glutathione, in vivo MEGA-PRESS experiments were conducted and various neuropsychological tests: cognitive performance, perceptual reasoning, working memory, processing speed and perceived stress scale were performed.
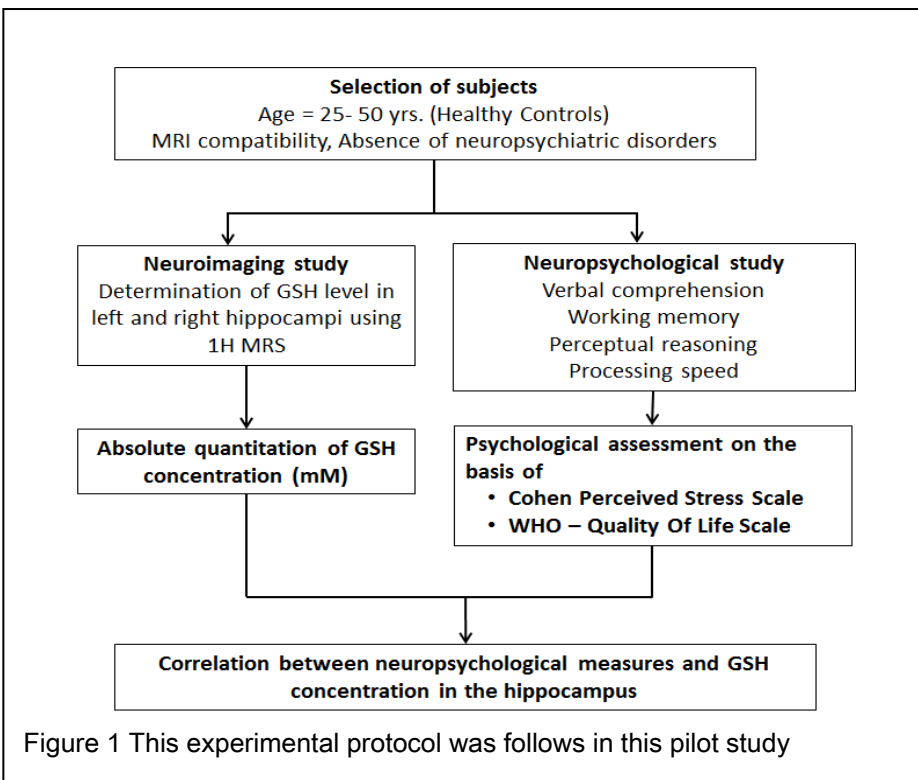
*Brain imaging study*

We have used 3T Philips MRI scanner equipped with state-of-the-art dual tuned ($^1$H/$^{31}$P) transmit and receive coil. Brain glutathione was detected using Mega-PRESS pulse sequence. The excitation of 180deg pulse was applied at 4.40 ppm.   The glutathione peak detected at 2.80 ppm was processed using in-house developed MATLAB based package "Kalpana" and quantified with reference to external phantom concentration. The GSH quantitation, the voxel of 25/25/25 mm$^3$ was placed in the respective brain region. For this single voxel experiment, for each region, it took 13.4 min per brain experiment time. Absolute glutathione concentration (from human brain) was determined with respect to external reference containing pure glutathione (Sigma Aldrich) in a
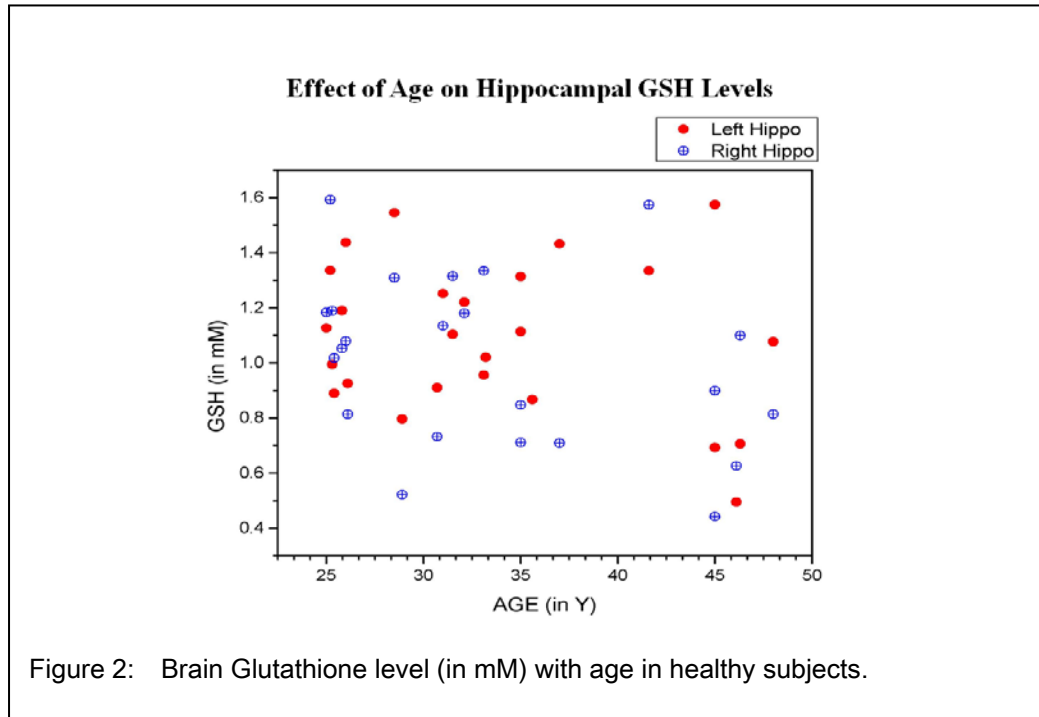
spherical phantom.

**For Neuropsychological tests:**

The following tests for verbal compression, working memory, perceptual reasoning and processing speed paper pencil tests were conducted. Each subject took more than one hour. In most of the cases, we have to give break for 20 minutes as subjects wants to take a break. The raw score was plotted against each subject age.



Figure 1 This experimental protocol was follows in this pilot study

**Results and Discussion:**



Figure 2:   Brain Glutathione level (in mM) with age in healthy subjects.

Neuropsychological profile of healthy subjects at various age.
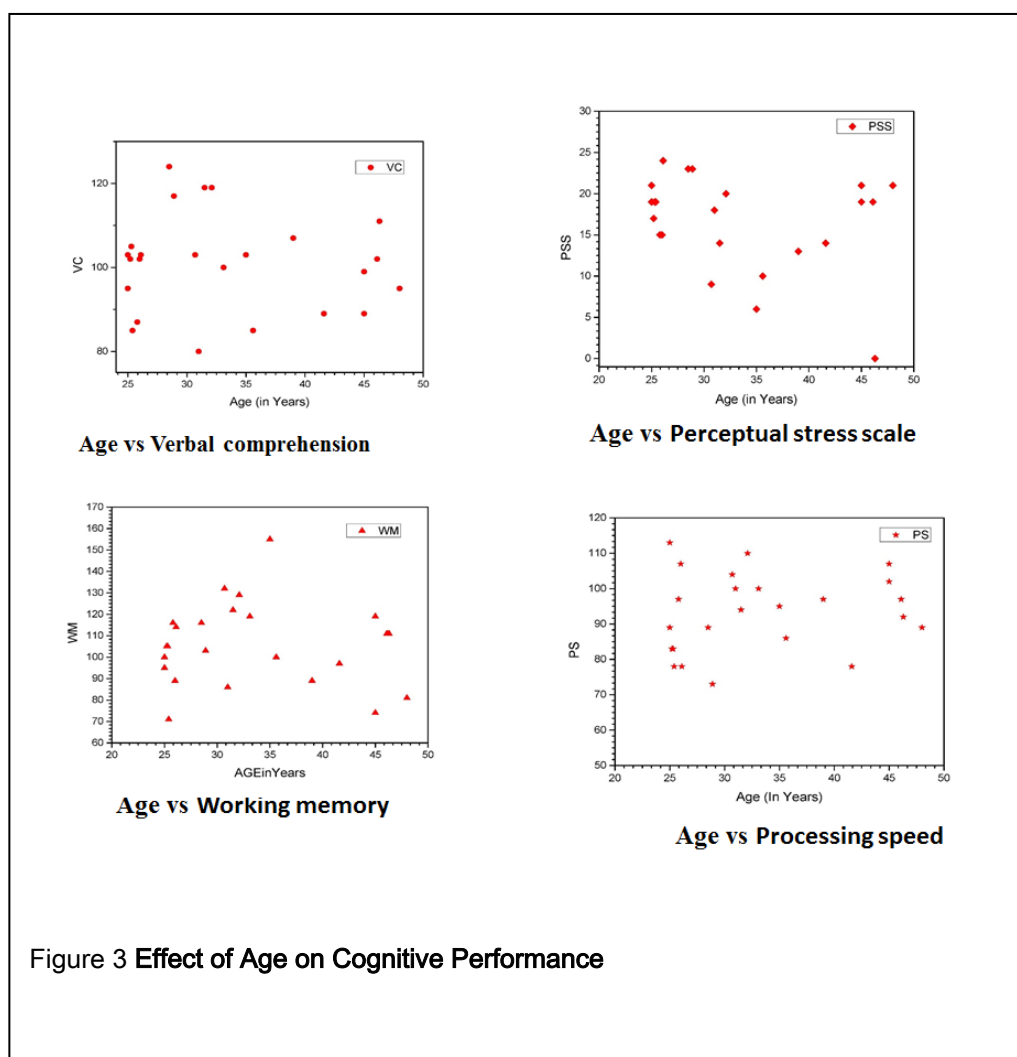
Figure 3 **Effect of Age on Cognitive Performance**

*Describe significant experimental and/or theoretical research advances or findings and their significance to the field and what work may be performed in the future as a follow on project. Fellow researchers will be interested to know what impact this research has on your particular field of science.*

This research opens up new direction in brain research where unique brain antioxidant (GSH) can be non-invasively detected, quantified and correlated with the cognitive performance. This pilot research clearly indicate that we should select subjects from 35 to 50 years of age and perform brain GSH level and computerized neuropsychological test with larger sample size.

**List of Publications and Significant Collaborations that resulted from your AOARD supported project:**

- The pilot data generated was presented twice at Wright-Patterson Air Force Base, Dayton Ohio

**Manuscript in Preparation**:

Age Related Depletion of Brain Anti-oxidants Glutathione and its Impact on Neuropsychological Outcome- A Pilot Study (***Manuscript in preparation***)